REMARKS

Claims 1, 26, 56-58, 60-66, 69, 70, 72, 73, 75-79, 81, and 86 are pending. Claims 2-25, 27-55, 58, 59, 61, 64, 67, 68, 71, 74, 80, and 82-85 have been cancelled without prejudice or disclaimer. Claims 1, 26, 56-57, 60, 62, 63, 69, 81, and 86 are amended herein. No new matter is added by the amendments. Upon entry of the present amendment, claims 1, 26, 56-57, 60, 62-63, 65-66, 69-70, 72-73, 75-79, 81, and 86 will be pending.

Amendment and cancellation of the claims herein are not to be construed as an acquiescence to any of the rejections/objections made in the instant Office Action or in any previous Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the claims as originally filed, or substantially similar claims in one or more subsequent patent applications.

Support for the Amendments

Support for the amendments to claims can be found throughout the specification and claims, as originally filed and are discussed in detail herein.

Claim 1 as amended defines the Z group as being phenyl and provides for W,V and Y forming a 5 or 6 membered ring fused with Z. Support for these amendments is provided by pending claim 69 and original claim 1 as filed. Related amendments have been proposed to claims 56-57, 60, 62, 69 and 81.

Claim 26 as amended defines the claimed method as being a method for inhibiting dynamin-dependent endocytosis in the cell or synaptosome. Support for this amendment is found in the specification, for example, at least at page 4, lines 6-9.

Claim 62 has been amended to define *W, V and Y* as forming the 6 membered ring fused with Z. Support for this amendment is provided by claim 1.

Claim 63 as amended defines Y as being cyano, nitro, amino or hydroxyl. Support for this amendment is provided by claim 1.

Claim 86 as amended defines the claimed method as being a method for prophylaxis or treatment of epilepsy in a mammal. Support for this amendment is at least found in claim 50 as originally filed.

Amendment to claims 60, 63, 65, and 67 is to correct the dependency of the claims resulting from the cancellation of claims. No new matter is added by the amendments.

Rejection of Claims 1, 26, 56-58, and 60-66, 69, 70, 72, 73, 75-79, 81, and 86 Under 35 U.S.C. §112, First Paragraph

The Office Action rejects claims 1, 26, 56-58, and 60-86 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with both the written description and enablement requirements. For the reasons detailed below, Applicants respectfully disagree and traverse the rejections.

Written Description Rejection

The Office rejects claim 86 as allegedly lacking an adequate written description for reciting the term "prodrug." Specifically, the Office Action alleges

> ... the issue here is not whether the artisan knows what a prodrug is, but whether it was described in regard to the instant Formula I. Because there is no support for "prodrug" in the specification, it is not clear that applicant had possession of "prodrug," in general of Formula I. (Office action mailed March 3, 2009, page 2).

For the reasons detailed below, Applicants respectfully disagree with the Examiner's assertion that "prodrugs" are not enabled by the disclosure of the invention provided by the specification, and that the Applicant "makes no correlation between structure and function" of prodrugs.

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention (M.P.E.P. 2163.04 II.A.3(a)).

As stated in the instant specification, "A prodrug may for example be inactive when administered but undergo *in vivo* modification into the active compound that binds to

dynamin such that the GTPase activity of the protein is inhibited, as a result of cleavage or hydrolysis of bonds or other form of bond modification post administration. Preferably, the prodrug form of the active compound will have greater cell membrane permeability than the active compound thereby enhancing potency of the active compound." (page 16, lines 19-24). Moreover, as also stated, "A prodrug may also be designed to minimize premature *in vivo* hydrolysis of the prodrug external of the cell such that the cell membrane permeability characteristics of the prodrug are maintained for optimum availability to cells and for systemic use of the compound" (page 16, lines 25-27).

The specification not only clearly exemplifies a range of prodrug forms, but also provides specific exemplification of the provision of such prodrugs to the skilled artisan, as well as their utility. In particular, Applicants point out that not only do the disclosures provided at page 16, lines 13-27, and Examples 3 and 4 of the specification describe a large variety of prodrug types that may be utilized in embodiments of the invention, but the disclosure at page 16 specifically indicates that the exemplified prodrug groups can be covalently linked to free amino, hydroxyl and carbocylic groups of a compound of Formula I.

In support of the specification's compliance with the written description requirement, Applicants submit herewith a declaration under Rule 1.132 ("Declaration") from Prof. Robinson, an inventor of the present application and an expert in the field. The Declaration at paragraphs 7-9 indicates that it is clear from the context of the present invention that the term "prodrug" is a compound which is converted or modified *in vivo* to a compound of Formula I. The requirement is that the prodrug provide a compound of Formula 1 *in vivo*. As the Declaration also states, the provision of such prodrugs was a matter of routine experimentation at the priority date of the Application.

The Examiner has also maintained that it was unclear that the Applicant had possession of a prodrug. Applicants respectfully draw the Examiner's attention to paragraph 10 of the Declaration, which shows that the prodrugs listed in the specification at Table 3 page 46, had been provided and characterized. Importantly, the Declaration describes that those prodrugs are hydrolyzed in serum to release the active compound of Formula I and that this blocks endocytosis in cultured cells.

In view of Applicants' disclosures, and in view of the art-recognized meaning of the term "prodrug" at the time of filing, one of ordinary skill in the art would have recognized Applicants' possession of the claimed invention at the time of filing. This possession of the claimed invention is also evidenced by the Declaration submitted herewith.

Thus, the application complies with the written description requirement of 35 U.S.C. § 112, first paragraph. Accordingly, the written description rejection should be withdrawn.

Enablement Rejection

The Office Action rejects claims 1, 26, 56-58, 60-66, 69, 70, 72, 73, 75-79, 81, and 86 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Office Action alleges

> The specification does not reasonably provide enablement for prophylaxis or treatment of disease mediated by dynamin-dependent endocytosis." (Office action mailed March 3, 2009, page 3).

As an initial matter, claims 58, 61, and 64 are cancelled without prejudice or disclaimer, thereby rendering the rejection moot as applied to these claims. Regarding claims 1, 26, 56-57, 60, 62, 63, 65, 66, 69, 70, 72, 73, 75-79, 81, and 86, Applicants respectfully disagree and traverse this rejection for the reasons set forth below.

The standard for enablement set forth in 35 U.S.C. 112, first paragraph, requires that Applicants provide a description of the invention sufficient "to enable any person skilled in the art to which it pertains . . .to make and use" the invention. The proper test of enablement is set forth in *United States v. Telectronics, Inc.*, (857 F.2d 778, 785, 8 USPQ2d at 1217, 1223 (Fed. Cir. 1988)):

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation.

Applicants claims are directed to methods for inhibiting the GTPase activity of dynamin in a cell or synaptosome, and to methods for treating or preventing epilepsy. Applicants respectfully disagree with Examiner's view that the specification is not enabling for the prophylaxis or treatment of a disease or condition mediated by dynamin-dependent endocytosis, and epilepsy in particular (i.e., Claim 86 has been amended to recite "a method for prophylaxis or treatment of epilepsy in a mammal"). The Office Action at page 4 states:

> While the present claims encompass preventing epilepsy, Applicant's data merely shows support for treatment through *in vitro* experimentation.

Thus, Applicants' have demonstrated an *in vitro* utility that reasonably correlates with an *in vivo* activity being claimed. Regarding the Office's stance on enablement when such a correlation is relied upon, M.P.E.P. §2164.02 is clear that "a rigorous or an invariable exact correlation is not required," citing *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and **therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.** (Citations omitted.) [Emphasis added.]

Because the examples in the specification demonstrate an *in vitro* utility that reasonably correlates with an *in vivo* activity, the claims are at least enabled according to this standard. Therefore, the claims are consistent with the scope of the disclosure of the application, which would convey to one of skill in the art "how to make and use" the invention. The mere fact that Applicants have not presented *in vivo* data does not make the present application non-enabling for the prophylaxis or treatment of a disease or condition mediated by dynamin-dependent endocytosis, and epilepsy in particular.

Nevertheless, the Declaration of Prof. Robinson submitted concurrently herewith describes *in vivo* data supporting Applicants' claims to a method of treating epilepsy. The

Declaration at paragraphs 15-17 states that effective inhibition and treatment of seizures in a mouse model of epilepsy were obtained by both compounds of Formula I and prodrugs of Formula I that are described in the instant specification, as part of a study conducted by the National Institutes of Health (**NIH**) at Bethesda, Maryland, United States under The Anticonvulsant Screening Program (**ASP**) of the NIH.

Accordingly, it is submitted that using an internationally standard animal model, the Declaration clearly shows *in vivo* efficacy of compounds of Formula I to inhibit endocytosis for the treatment of a disease or condition, and epilepsy. Thus, the Declaration shows that the compounds are enabled for the treatment of endocytosis for the treatment of a disease or condition epilepsy in particular, as specifically claimed in amended claim 86.

Claim 1, as currently amended, recites "a method of inhibiting the GTPase activity of dynamin in a cell or synaptosome." Claims 26, 56-58, and 60-66, 69, 70, 72, 73, 75-79, and 81, which directly or indirectly depend from claim 1 also incorporate this feature. It is submitted the specification clearly teaches the inhibition of GTPase activity of dynamin in a cell or synaptosome, as recited in claim 1 as amended; and the inhibition of dynamin-mediated endocytosis in a cell or synaptosome, as recited in claim 26 as amended.

The specification as filed presents working examples of methods for inhibiting the GTPase activity of dynamin in a cell or synaptosome. Specifically, Example 1 of the specification as filed (page 22, line 3 to page 30, line 10) discloses that bis-tyrphostin inhibited the GTPase activity of both dynamin I and dynamin II (see page 26, lines 10-27 of the specification as filed). Indeed, the inhibition of both dynamin I-mediated synaptic vesicle retrieval in synaptosomes and dynamin II receptor-mediated endocytosis in cells by bis-tyrphostin is at least exemplified, for example, at page 28, line 9 to page 29, line 2 and page 29, lines 3-13. Applicants respectfully submit that the specification fully enables a method for inhibiting the GTPase activity of dynamin in a cell or synaptosome (claim 1 as currently amended); and inhibiting dynamin-mediated endocytosis in a cell or synaptosome (claim 26 as currently amended).

Applicants also respectfully disagree with the Examiner's assertion that the specification is not enabling for the use of the broad genus of compounds of Formula I. Nevertheless, without acquiescing in any way to the rejection and solely to expedite prosecution of the application, Applicants have amended the claims so that the scope of compounds encompassed by Formula I is narrowed. Specifically, claim 1 as amended now recites the Z group as being a phenyl group and provides for the possibility of W, V and Y forming a ring of the defined size fused with the phenyl group. Support for this amendment is at least found, for example, at claim 50 as originally filed, and in the specification at page 13, line 31 to page 15, line 5, and at page 40, lines 5-7.

Rejection of Claims 1, 26, 56-58, 60-66, 69, 70, 72, 73, 75-78 and 81 Under 35 U.S.C. §103(a)

Gazit *et al* (*J. Med. Chem*, 1996) in view of Ahn *et al* (*J. Biol. Chem*, 1999)

The Office rejects claims 1 and 79 under 35 U.S.C. §103(a) as being obvious over Gazit *et al.* (Journal of Medicinal Chemistry 1996; hereinafter "Gazit") in view of Ahn *et al.*, (*Journal of Biological Chemistry* 1999; hereinafter "Ahn"). As detailed below, Applicants respectfully disagree and traverse the rejection.

To establish a *prima facie* case of obviousness, the Examiner must establish that the prior art included each element claimed (M.P.E.P. 2143). In addition, "[a] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.* 167 L. Ed. 2d 705, 712. The Supreme Court in *KSR* reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co.* (383 U.S. 1, 148 USPQ 459 (1966)), but stated that the Federal Circuit had erred by applying the teaching-suggestion-motivation (TAM) test in an overly rigid and formalistic way.

Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting

In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carmella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractoriness, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). The combination of Gazit and Ahn fail to support the rejection of the claims as obvious because the references fail to describe each element of the claimed invention.

Pending claim 1 of the present application is directed to a method of *inhibiting the GTPase activity* of dynamin in a cell or synaptosome, comprising contacting the cell or synaptosome with an effective amount of a compound of Formula I or a physiologically acceptable salt thereof. Importantly, the claim requires the treatment of the cell or synaptosome with the compound *to inhibit the GTPase activity* of dynamin, and is based on the finding that compounds of Formula I are direct dynamin GTPase inhibitors. That is, they act directly on the protein to exert their effect. It is submitted that none of the cited references alone or in combination teaches or suggests that such compounds are dynamin GTPase inhibitors and provide no motivation to use them for this purpose.

The Examiner posits that Gazit and Ahn "provide a link between dynamin activity and Bis-T23" (a compound of Formula I). Applicants respectfully disagree with this conclusion. Gazit provides a disclosure of the use of certain dimeric tryphostins as inhibitors of protein tyrosine kinases (PTK), a type of enzyme that differs completely from the *GTPase* dynamin. Applicants reiterate that Gazit is *entirely silent in relation to dynamin* and provides no teaching whatsoever that dimeric tyrphostins described in Gazit may *inhibit the GTPase activity* of dynamin, let alone the use of dimeric tryphostins or more generally compounds of Formula I for inhibition of dynamin-dependent endocytosis or the prophylaxis or treatment of epilepsy.

The Examiner has cited Ahn to remedy this deficiency of Gazit. Applicants point out that Ahn merely teaches that c-Src phosphorylation of particular *tyrosine residue(s)* of dynamin occurred in parallel with clathrin mediated G-protein coupled receptor

endocytosis. Ahn does not utilize any GTPase inhibitors or a compound of Formula I of the present application, nor does Ahn teach that endocytosis is reliant on tyrosine phosphorylation of dynamin. Rather, Ahn indicates solely that c-Src mediated signaling through tyrosine phosphorylation is involved in endocytosis and this includes, among other things, dynamin. As is apparent to one skilled in the art, endocytosis is mediated by many pathways that do not involve c-Src tyrosine kinase or indeed, any tyrosine kinase.

Ahn concludes in the last paragraph that the results establish that c-Src-mediated tyrosine phosphorylation of dynamin provides *one mechanism* by which β4-AR regulates its internalization and MAP kinase signaling. c-Src and epidermal growth factor receptor (EGFR) signaling were known at the time of the work of Ahn to involve complex signaling networks involving a very large number of proteins. For example, Wilde *et al.* ("EGF receptor signaling stimulates SRC kinase phosphorylation of clathrin, influencing clathrin redistribution and EGF uptake." *Cell* 96:677-687, 1999; a copy of which is submitted herewith) describes the c-Src-mediated phosphorylation of clathrin heavy chain (CHC). The inhibition of c-Src using the specific Src family kinase inhibitor PP1 was reported by Wilde to inhibit clathrin phosphorylation and delay EGF endocytosis.

The work of Ahn is related to the Wilde study in simply showing yet another effect of c-Src inhibition is the reduction of dynamin phosphorylation. The mere observation that a reduction of dynamin phosphorylation correlates with c-Src inhibition does not indicate a direct action on endocytosis. Neither Ahn nor Wilde teaches that effects on endocytosis are directly mediated by only CHC or dynamin, and these disclosures merely show that c-Src acts on many proteins. In particular, Applicants submit that at the priority date of the present application:

a) The data of Ahn did not show any effect on dynamin GTPase activity;

b) There was no specific evidence or reason to believe that phosphorylation of dynamin as described by Ahn inhibited/blocked endocytosis directly; and

c) There was no evidence that the effects reported by Ahn were mediated by dynamin directly.

As stated above, Ahn does not teach that any compound used in that study directly inhibits dynamin GTPase activity, and the reference exclusively refers to indirect signaling mediated upstream of dynamin. This also applies to the disclosure provided by Wilde. Moreover, neither Ahn nor Gazit (or Wilde) directly or indirectly measured dynamin GTPase activity, nor hinted that the compounds they utilized might directly affect such activity.

Specifically, Ahn does not teach any **causal connection** between the use of a c-Src inhibitor and *the inhibition of dynamin GTPase activity*, as further evidenced by Wilde. Indeed, neither Ahn nor Wilde in any way teaches or suggests that the GTPase activity of dynamin as a target for a c-Src inhibitor.

Further, Applicants cite *more recent* literature (Tan *et al., Nat. Cell. Biol.*, 2003, hereinafter "Tan"; and Tomizawa *et al., J. Cell Biol.*, 2003, hereinafter "Tomizawa"; both submitted in the Response dated December 1, 2008) showing that the disclosure provided by Ahn using the artificial cell model cannot be generalized to neuronal cells. The artificial cell model of Ahn, which involved the introduction of a neuron-specific dynamin I gene into a non-neuronal cell, is not representative of the behavior and activity of dynamin I in neuronal cells.

In direct contrast to Ahn, Tan teaches that phosphorylation of particular serine residues on dynamin I by cyclin-dependent kinase (Cdk5) *is essential* for synaptic vesicle endocytosis (SVE) in neurons. Cdk5 is a serine/threonine kinase *and not* a protein tyrosine kinase (PTK). e.g., c-Src. Importantly, Tan teaches that SVE is activated by a calcineurin-mediated dephosphorylation event of serines and/or threonines *but not tyrosine amino acid residues* (page 701, Col. 1, line 1 to Col. 2, line 17). Tomizawa also teaches that phosphorylation of Thr 780 of dynamin by Cdk5 negatively regulates clathrin-mediated endocytosis of synaptic vesicles.

Nevertheless, both Tan and Tomizawa teach it is the activity of Cdk5 (*a serine/threonine kinase*, and **not a PTK**) that is central to dynamin-mediated endocytosis.

Hypothetically, were one to accept the validity of Tan and Tomizawa over Ahn, one *would not* consider the use of an inhibitor of PTK to inhibit a serine/threonine kinase such as Cdk5, an entirely different class of enzyme. In this way, Tan and Tomizawa ***teach away from the selection and use of a PTK inhibitor to inhibit dynamin GTPase activity or dynamin-mediated endocytosis***, especially for neuronal or brain function. Even so, serine/threonine kinases and PTKs are entirely different enzymes from GTPases and specifically, the dynamin GTPase.

Therefore, Applicants respectfully submit that one of ordinary skill in the art would not be motivated to target PTK to inhibit dynamin GTPase activity, in view of the teachings found in the art. Although Ahn observed a relationship between PTK and dynamin, Ahn's observation was an artifact of an artificial cell model expressing a dynamin transgene. Thus, in combining the cited references, the Examiner's reliance on PTK is misplaced. For the sake of argument, an artisan motivated by Ahn would be inhibiting a kinase that affects dynamin in the artificial cell model, but has not been shown to affect dynamin in neuronal cells. Therefore, the disclosure of Ahn would not provide any expectation of success nor lead to possession of the method as currently claimed.

As of the filing date of the application, there was no teaching or suggestion that dimeric tyrphostin or other compound of Formula I of the present claims inhibited dynamin GTPase activity and thereby could mediate endocytosis in a cell or synaptosome. Indeed, the use of such a compound is entirely contrary to any of the references described herein. It is well accepted that the use of hindsight is impermissible, and that the current point must be assessed by adopting the position of the artisan as at the priority date of the application in the absence of knowledge of the invention. It is only with the benefit of hindsight that the Examiner seeks to combine the disclosure of Ahn with the teachings of Gazit. Nevertheless, there is no teaching suggestion or motivation to combine the references in the manner suggested by the Examiner to arrive at the invention being claimed.

Accordingly, Applicants respectfully request withdrawal of the rejections of claims 1 and 79 over Gazit in view of Ahn.

Gazit et al (J. Med. Chem, 1996) in view of Jassar et al (J. Med. Chem., 1997)

The Office rejects claims 26, 56-58, 60-66, 69, 70, 72, 73, 75-78 and 81 under 35 U.S.C. §103(a) as being obvious over Gazit in view of Jassar *et al.* (Brain Research 775"127-133, 1997; hereinafter "Jassar"). Applicants have cancelled claims 58, 61, and 64 without prejudice or disclaimer, thereby rendering the rejection moot as to those claims. Regarding claims 26, 56-57, 60, 62, 63, 65, 66, 69, 70, 72, 73, 75-78 and 81, Applicants respectfully disagree and traverse the rejection as detailed below.

In view of the foregoing arguments regarding the rejections under 35 U.S.C. § 103 over Gazit in view of Ahn, Applicants once again submit that Gazit provides no teaching regarding the inhibition of *GTPase dynamin*. At best, Gazit describes certain dimeric tryphostins as inhibitors of protein tyrosine kinases (PTK). However, as noted in the foregoing arguments, PTK was implicated in an artificial non-neuronal cell model but has not been shown to regulate dynamin in neuronal cells.

Jassar also does not teach the inhibition of *GTPase dynamin*. Instead, Jassar relates to a study purporting to show that phosphorylation is important for the activation and long term maintenance of $GABA_A$ receptors and that tyrosine kinase modulates GABA mediated neurotransmission.

Jassar reports that a *monomeric* tyrphostin B44(-) attenuated $GABA_A$ receptor responses. The Examiner has asserted Jassar suggests that the monomeric tyrphostin, tyrphostin B-44, would be useful in treating epilepsy, and that Gazit teaches that dimeric tyrphostins have improved efficacy over monomeric tyrphostins. As such, the Examiner asserts that the artisan would have been motivated to use dimeric tyrphostin to inhibit endocytosis and treat epilepsy, based on this improved efficacy. Applicants respectfully disagree.

Firstly, the assertion that the dimeric tyrphostins described by Gazit have improved efficacy is not supported by the disclosure of Gazit. Specifically, Applicants submit the dimeric tyrphostins described by Gazit were *not* more potent (nor were they claimed to be) than the monomeric tyrphostins on which they were based. Rather the dimeric tyrphostins were mostly up to 10 fold less potent, the very best at the time being about equally potent. For a summary of the previous optimal monomeric tyrphostins,

Applicants invite the Examiner's attention to Levitzki and Gazit ("Tyrosine kinase inhibition: an approach to drug development." Science 267 (5205):1782-1788, 1995; hereinafter "Levitzki"; a copy of which is being submitted herewith).

Gazit disclosed the *ability* to make the monomeric tyrphostins dimeric, *rather than* an attempt at improved potency over monomeric tyrphostins. Indeed, Applicants believe this is the reason why the Gazit research team in later studies subsequently focused on the development of *monomeric* tyrphostins and abandoned the dimeric tyrphostins, including compounds of the type of Formula I of the present application.

The Examiner asserts that the dimeric tyrphostins described in Gazit were somehow improved. But nowhere in Gazit is a conclusion that these compounds are more active than monomeric tyrphostins. Rather, Gazit concludes the dimeric tyrphostins described are more active than previous attempts at making *dimeric* tyrphostins (see Gazit, page 4908, right column, last paragraph of discussion). Apart from this discussion comment in Gazit, there are no teachings to the improved potency or efficacy of dimeric tyrphostins compared to dimeric tyrphostins.

Secondly, Jassar is a study relating to whether $GABA_A$ receptor function in DBB neurons is modulated by PTK activity. No part of the Jassar study examined epilepsy, dynamin or endocytosis. Jassar merely speculates at the end of the article (see page 133, Col. 1, lines 1-13):

> Modulation of $GABA_A$ responses by PTK activity ***may be important*** in maintenance and regulation of physiological functions of basal forebrain neurons such as theta rhythm [18], automatic cardiovascular responses [12] and memory and learning mechanisms [2,5] which ***may require*** long term and tonic activation of $GABA_A$ receptors. ***A better understanding of cellular mechanisms underlying the actions*** **of a ubiquitous central inhibitory transmitter may have important therapeutic implications in conditions such as epilepsy where *GABA neurotransmission is aberrant*.** [Emphasis added.]

Accordingly, the focus of Jassar is the regulation/mechanism of action of the $GABA_A$ receptor with a view to obtaining *a better understanding of the role of the receptor*

in a range of physiological functions of neurons in the forebrain. Epilepsy is mentioned but this is in the context of simply noting that GABA neurotransmission is aberrant in that condition and suggesting that ***a better understanding*** of the regulation of GABA neurotransmission and the mechanisms involved ***is required to develop*** *a* therapy for that and other conditions.

Thus, it is clear that Jassar did not recognize or consider that inhibition of dynamin GTPase activity *provides* a method for the prophylaxis or treatment of epilepsy. The statements of Jassar provide little guidance, and merely provide an invitation to further experimentation. For example, Jassar states that GABA neurotransmission is aberrant in epilepsy, but this does not even begin to address whether GABA neurotransmitter or $GABA_A$ receptor is involved in epilepsy, much less how one could modulate the $GABA_A$ receptor to treat epilepsy. Even assuming *arguendo*, one were to use a dimeric tyrphostin described in Gazit to attenuate $GABA_A$ receptor responses, what effect on epilepsy would this have? The teachings of the cited art and the motivation to combine them is lacking to arrive at Applicants' claimed invention. As such, it is submitted that Jassar's reference to epilepsy is simply the result of a series of speculations made in the citation, that are not supported by the evidence presented by Jassar. Such an invitation to experiment further based on speculations cannot provide one or ordinary skill in the art with a reasonable expectation of success in practicing the claimed invention.

Hence, Jassar simply indicates that PTK activity has a role in the regulation of the $GABA_A$ receptor function in intact neurons. This is entirely distinct from suggesting the use of dimeric tyrphostins of the type described in Gazit or other inhibitor *to inhibit* the GTPase activity of dynamin to in turn inhibit endocytosis and provide a therapy for epilepsy.

In conclusion, Applicants submit that Jassar provides no motivation to select a dimeric tyrphostin of the type disclosed in Gazit to inhibit the GTPase activity of dynamin in a cell or synaptosome as now claimed or for that matter, the prophylaxis or treatment of epilepsy in particular. Again, it is only with the benefit of hindsight that the Examiner seeks to combine the disclosures of Jassar with those of Gazit, and even by doing so, it is

submitted the combination still does not teach each and every element of the invention as currently claimed.

Accordingly, Applicants respectfully request withdrawal of the rejections of claims 26, 56-58, 60-66, 69, 70, 72, 73, 75-78 and 81 over Gazit in view of Jassar.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the application with claims 1, 26, 56-57, 60, 62-63, 65-66, 69-70, 72-73, 75-79, 81, and 86 presented herein. In advance of the issuance of a final Office Action, Applicants invite the Examiner to call the undersigned at the telephone number indicated below to schedule an interview.

Dated: September 3, 2009

Respectfully submitted,

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